

A Study on Histogenesis of Fetal Suprarenal Gland in Various Gestational Age Groups: A Cross-Sectional Study from Tamil Nadu

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Abstract

Background: The suprarenal glands are located retroperitoneally near the posterior abdominal wall at the eleventh—twelfth thoracic vertebrae level. Each gland consists of an outer cortex and an inner medulla. The current study aims to examine the microscopic anatomy of developmental changes in the fetal suprarenal gland in various fetal age groups. **Material and Methods:** This study was an institution-based observational study conducted in the Department of Anatomy, Thanjavur Medical College, Thanjavur. In this study, 25 dead fetuses with gestational ages ranging from 12 to 32 weeks were obtained from the Obstetrics and Gynecology Department at Thanjavur Medical College. These fetuses were the products of pregnancies that were terminated under the MTP Act of India, 1971. **Results:** We found that the medulla was poorly characterized between 12 and 16 weeks, while the embryonic suprarenal cortex showed up as two layers: the permanent cortex and the fetal cortex. By the 22nd week, the transitional zone appeared, and the medulla was identifiable. The fetal cortex began to shrink around weeks 22 and 24. By 29 to 32 weeks, zona fasciculata and zona glomerulosa were formed from the permanent cortex's cells. The fetal cortex and permanent cortex have a 1:4 ratio. Throughout the whole development process, this was upheld. **Conclusion:** Three separate zones—the zona glomerulosa, zona fasciculata, and the fetal zone—could be distinguished in the microscopic examination of the fetal suprarenal gland. This study provides insights into suprarenal gland development, aiding clinicians in understanding conditions like pheochromocytoma and adrenal diabetes.

Keywords: Fetal Cortex, Permanent Cortex, Neuroblastic, Nodules, Transitional Zone, Chromaffin Cells.

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INTRODUCTION

Suprarenal glands are paired structures situated in the upper pole of each kidney in the posterior abdominal wall. Bartholomaeus Eustachius described the suprarenal gland in 1563.^[1] Anatomically, each adrenal gland is enveloped by a capsule and comprises an outer cortex and inner medulla. The outer cortex is divided into three zones: zona glomerulosa, zona fasciculata, and zona reticularis, whereas the inner medulla is composed of anastomosing cords of chromaffin cells with large blood vessels.^[2]

In animals, stress response is significantly influenced by corticotropin-releasing factor (CRF) by regulating the hypothalamic-pituitary-adrenal axis (HPA). Corticotropin-releasing factor (CRF) leads to the release of glucocorticoids from the suprarenal cortex.^[3]

The human fetal adrenal gland originates from the adrenogonadal primordium and becomes distinguishable in humans by 7 to 8 weeks of gestation. The suprarenals emit cortisol in response to adrenocorticotrophic hormone (ACTH) as early as the 8th week of gestation. During fetal life, they principally produce steroids, including dehydroepiandrosterone (DHEA) and its sulfate (DHEAS), which serve as substrates for placental estrogen production.^[4,5]

The fetal adrenal, in conjunction with the placenta, plays a crucial role in regulating fetal steroid endocrinology, making

normal fetal development of the adrenals essential for post-natal health.^[6]

Starklowa et al were the first to describe the fetal cortex. The mesoderm of the posterior abdominal wall, which lies between the urogenital ridge and the root of the dorsal mesentery, gives rise to the adrenal cortex.

The Adrenal medulla is derived from the neural crest cells. During the fetal period, the fetal cortex, the human adrenal gland during pregnancy, vanishes within the first year of life. The permanent and foetal cortex are the zones that make up the fetal suprarenal gland by 12 weeks of pregnancy. Three zones comprise the fetal adrenal gland by 13–36 weeks of pregnancy. The fetal cortex, transitional zone, and permanent cortex are these. By the tenth week of intrauterine life, chromaffin cells begin to form.^[7-9]

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MATERIALS AND METHODS

This institution-based cross-sectional study was conducted in the Department of Anatomy, Thanjavur Medical College, Thanjavur. Twenty-five deceased fetuses with gestational ages ranging from 12 to 32 weeks, which were the result of pregnancies that were terminated under the MTP Act of India, 1971, and stillbirths, were collected from Thanjavur Medical College's Obstetrics and Gynecology Department in Thanjavur for the study.

Ethical committee approval was obtained from the Institutional Ethical Committee, Thanjavur Medical College, Thanjavur. Twenty-five healthy fresh fetuses of various gestational age groups, from 12 weeks to 32 weeks, were acquired from the Department of Obstetrics and Gynecology, Thanjavur Medical College, Thanjavur, Tamil Nadu, following informed consent. The fetuses were the product of terminated pregnancies and stillbirths. Fetuses free from gross anatomical abnormalities were selected for the study. The samples of the fetal adrenals were obtained by meticulous dissection and fixed with 10% formalin for 10 days. They were grouped into I, II, III, IV, and V based on gestational age. The samples were processed for routine Histopathological procedures and Hematoxylin and Eosin staining. Stained slides were studied under a binocular Research Light Microscope (Magnus) and analyzed using 4x, 10x, and 40x Objectives. The data were entered and analyzed using Microsoft Excel.

RESULTS

The study included 25 dead fetuses aged between 12 and 32 weeks. The majority of the deceased fetuses belonged to the age group between 25-28 weeks (44%), followed by fetuses aged 17-20 weeks (24%). In our study, 12% of the fetuses belonged to the age group between 12 and 16 weeks and 21 and 24 weeks, while 8% of the deceased fetuses were aged between 29 and 32 weeks

The following titles were used to examine how different layers appeared in different gestational age groups:

1. Capsule
2. Adrenal Cortex
3. Adrenal Medulla.
4. Immunohistochemistry

Capsule: At 12 weeks of gestation, we noticed that the capsule could be identified under light microscopy. Blood vessels were visible, and the capsule thickened between weeks 17 and 20 of pregnancy. Lymphocytic infiltration was also seen. The capsule and the trabeculae were fully formed between weeks 21 and 25 of pregnancy.

The collagen fibers and fibroblasts were also seen. The thick, well-developed capsule that envelops the whole gland was observed during 26 to 28 weeks of gestation. Trabeculae extend from the capsule from 29 to 32 weeks of gestation, carrying the sinusoidal blood vessels with them.

Adrenal Cortex: Among the fetuses in the first group, the cortex was observed to be divided into two zones. The permanent or definitive cortex is the superficial, narrow zone with darkly staining basophilic cells. The permanent cortex comprises one-tenth of the entire brain and has tiny,

basophilic cells.

Lightly discolored. Deep within the permanent brain is the fetal cortex. Large, polyhedral fetal cortical cells with vesicular and eosinophilic nuclei were seen. 9/10 of the entire cortex comprises layers that are 7 to 8 thick. The fetal cortex was bulkier with increasing gestational age in the specimens in our study.

In the second group, darkly stained superficial zone showed clusters of cells arranged in the form of a semilunar arch-like pattern representing the future. Cells with zona glomerulopathy were grouped in dense columns toward the fetal cortex's outer zone. It occupies 1/9th of the total cortex. Large, pale-staining eosinophilic cells dominate the deeper fetal zone.

The cells were six to seven layers thick and organized in a fasciculate reticular pattern. It takes up 8/9 of the entire cortex.

In the third group, the narrow Superficial zone showed a glomerular-like pattern and was separated by capillaries. Trabeculae extended from the capsule.

Cords of cells were observed extending from the permanent cortex into the fetal cortex at certain locations at the confluence of the permanent and fetal zones. This zone was referred to as the transitional zone. The cells of the transitional zone were intermediate in size and densely packed. The thickness of fetal cortical cells started to reduce.

The definitive cortex's thickness gradually rises in the fourth group, beginning around 25 weeks. A glomerular/arch/acini pattern was observed. Towards the fetal zone, cells of the definitive cortex were arranged in rows in a fascicular manner, and a sinusoidal space was found in between. The cortical cells of fetuses have a noticeable sponginess. This spongy look indicates the fetal cortex's involution.

In the fifth group, the permanent cortex underwent differentiation into two layers: zona fasciculata and zona glomerulosa. And its cells were arranged in a typical arched/glomeruli-like arrangement. It takes up one-fourth of the entire cortex. Cells that are one or two cells thick make up the zona fasciculata.

There are sinusoidal intervals between them, and they are grouped fascicularly. Fetal cortical cells were further reduced. It took up three-quarters of the entire cortex.

Adrenal medulla: Among the fetal specimens with 12 to 16 weeks of gestational age (Group I), the adrenal medulla was identifiable by the presence of a blood vessel at the center of the fetal adrenal gland. A solitary neuroblastic nodule was found to invade the capsule. Cells of the neuroblastic nodules are small, round, and darkly stained nuclei.

The sinusoidal spaces were identifiable among the fetal specimens aged 17 to 20 weeks (Group II). Numerous neuroblastic nodules seemed scattered throughout the gland.

The sinusoidal spaces were filled with blood in the fetal specimens of 21 to 24 weeks of gestational age (Group III). Neuroblastic nodules are dispersed throughout the gland.

Among the fetal specimens with 25 to 28 weeks of gestational age (Group IV), the number of neuroblastic nodules started to decrease, and a greater number of chromaffin cells were seen around the central medullary vein.

In the fetal specimens with 29 to 32 weeks of gestational age (Group V), the large blood vessels were seen at the center of the medulla, called the central vein. Chromaffin cells have pale staining cytoplasm and vesicular, round to oval nuclei.

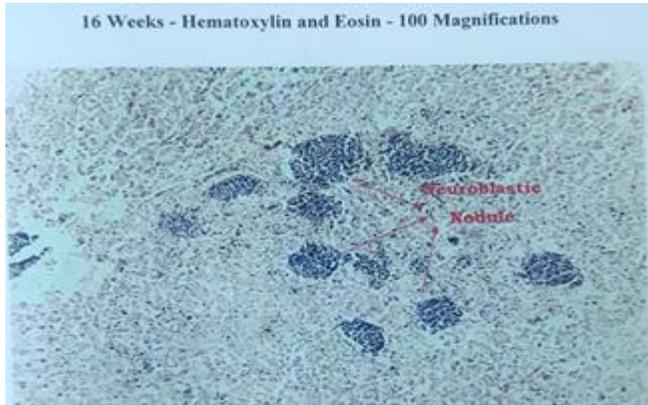


Figure 1: 16 weeks – Hematoxylin and Eosin – 100 Magnifications

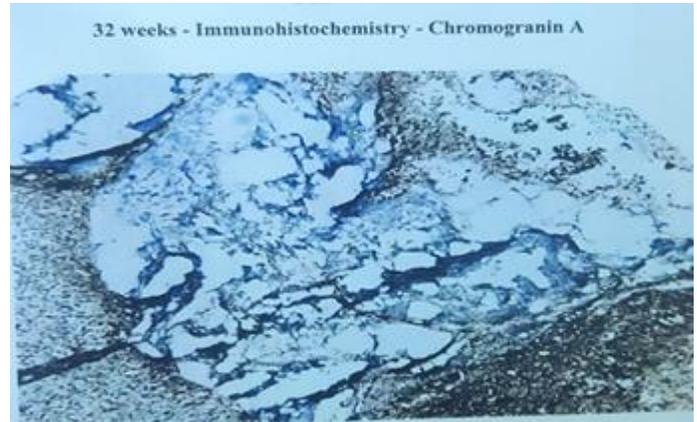


Figure 3: 32 weeks -Immunohistochemistry-Chromogranin A

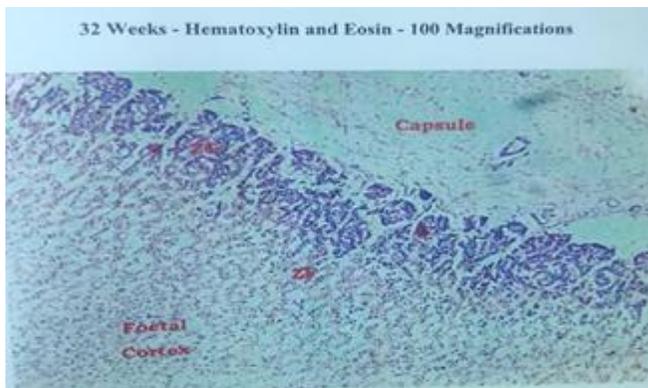


Figure 2: 32 weeks – Hematoxylin and Eosin – 100 Magnifications

Immunohistochemistry: Three distinct neural crest-derived cell types—chromaffin, ganglion, and sustentacular cells—comprise the adrenal medulla. Chromaffin cells constitute most of the adult adrenal medulla. It also contains a small number of ganglion cells interspersed among the chromaffin cells; the adrenal medulla also contains sustentacular cells, Schwann-like cells that closely envelop adrenal chromaffin cells without a basal lamina. The adrenal medullary sustentacular cells are demonstrated by their expression of S-100 protein. Chromaffin cells were characterized by immunohistochemical staining of chromogranin A. It is a major soluble protein in chromaffin granules. Chromaffin granules contained catecholamines, several neuropeptides, and a family of acidic proteins, the so-called granins (chromogranins/secretogranins).

Table 1: Gestation age of the observed fetal specimens (n=25)

Groups	Age in weeks	Frequency (n=25)	Percentage (%)
I	12-16 weeks	3	12
II	17-20 weeks	6	24
III	21-24 weeks	3	12
IV	25-28 weeks	11	44
V	29-32 weeks	2	8

Table 2: Microscopic observations among the observed fetal specimens (n=25)

Parameters	Capsule	Permanent cortex	Fetal cortex	Adrenal medulla
Group I (12-16 weeks)	Thin, ill defined	Narrow zone	Thicker	Neuroblastic nodules started invading the capsule
Group II (17-20 weeks)	Thicker	Semilunar/ arch pattern	Thicker	Numerous neuroblastic nodules are seen in cortex
Group III 21-24 weeks	Thicker and blood vessels are seen	Glomerular like pattern with sinusoidal spaces	Started reducing	Sinusoidal spaces were filled with blood
Group IV 25-28 weeks	Well-developed and surrounds entire gland	Acini pattern	Present but thin	Decreased number of neuroblastic nodules, increased chromaffin cells are seen
Group V 29-32 weeks	Trabeculae extending from it	Typical glomerular pattern	Started involuting	Chromaffin cells are seen, large central medullary vein seen

DISCUSSION

The present study was undertaken among the Twenty-Five dead babies of various gestational ages, ranging from 12 to 32 weeks, which were obtained from the Thanjavur Medical College's Obstetrics and Gynecology Department. The study aimed to identify and describe the microscopic anatomy of developmental changes in the fetal suprarenal gland in various fetal age groups. During the 6th week of intra-uterine

life, the suprarenal cortex begins as an aggregation of mesenchymal cells on each side of the embryo between the root of the dorsal mesentery and the developing gonad. The adrenal medulla is derived from an adjacent sympathetic ganglion, derived from neural crest cells. The weight of the fetal suprarenal gland is 10 to 20 times larger than that of an adult gland and is large compared with the kidneys. The gland rapidly grows through processes including cell proliferation and angiogenesis at the periphery of the gland, cellular migration, hypertrophy, and

apoptosis.^[10-12]

According to our research, the suprarenal gland capsule first appears as a thin strip around the 12th week of pregnancy, and as age advances, the thickness of the capsule likewise increases. The capsule has blood vessels and is thicker and more distinct around 16–22 weeks. Studies by Sangma et al also reported similar observations, but it takes until later in fetal life for the cortex to be completely encapsulated.^[13]

Our investigation found that the gland's vascularity progressively grew from the ninth to the thirty-second week of pregnancy. The research by Khayati and colleagues reported that fetuses with gestational ages between 12th to 28th weeks showed that as gestational age increases, so does the number of sinusoidal vessels.^[14] Rao et al., in their study, also reported similar observations.^[15]

The growth of the distinct fetal zone is mostly reflected in the rapid development and alterations within several zones of the fetal suprarenal gland. According to the results of the current study, the fetal cortex (i.e., 9/10 at 12 weeks, 8/9 at 20 weeks, and 3/4 at 32 weeks of gestation) provided a greater portion of the cortex. According to Benirschke et al., the fetal cortex developed four out of five times the adrenal cortex.^[16] The fetal cortex predominantly consisted of polyhedral cells, which were large in size. These cells contained a round nucleus surrounded by cytoplasm filled with eosinophils. Our findings were in concurrence with the observations of Rao et al, Benirschke et al, Turkel et al, and Mesiano et al.^[15-18]

According to the current study, Capillaries divided the cells in the fetal adrenal cortex outer region, which were organized in longitudinal columns. Cells in the interior region were structured as a network with sinusoidal voids interspersed. Uotila et al had observed that the fetal cortex of the suprarenal gland consisted of a fasciculoreticular layer, which was observed from the 7th week of development, according to the configuration of fetal cortical cells.^[19]

Sangma et al,^[13] and Benirschke et al,^[16] have documented that the examination of the cortex showed that One-fifth of the entire adrenal tissue was made up of the definitive cortex. Studies by Benirschke et al,^[16] Turkel et al,^[17] and Mesiano et al,^[18] observed that the definitive cortex contained small and polygonal cells. The cells contained euchromatic nuclei surrounded by a cytoplasm that contained basophils. Our observations in the present study were also in line with the findings of the studies above.

Sangma et al,^[13] and Mesiano et al,^[18] observed that the cells in the definitive cortex appeared as the adult zona glomerulosa between the 28th and 30th week of gestation. In our investigation, we found that by week 12, the definitive cortex's cells were composed of the adrenal cortex's tenth part. At the 28th week, it was 1/9th, and at the 32nd week, it was measured to be 1/4th.

The suprarenal gland's transitional zone consists of cells running from the definitive cortex to the fetal cortex. These cells are finger like column of cells. Our study observed that these cells appeared among the fetuses with a gestational age of more than 21 weeks. Observations by Sangma et al,^[13] and Mesiano et al,^[18] were similar to our findings. At the same time, by the fourteenth week of pregnancy, McNutt et al. had

noted the appearance of the transitional zone between the permanent and fetal zones.^[20]

The medulla of the suprarenal gland is formed by the neural crest cells. At the 12th week of gestation, the neuroblastic cells appear in the suprarenal cortex. Various anatomists have used different terminologies for these cells; they are neuroblastic nodules (Turkel et al),^[17] pheochromoblast (Coupland et al),^[21] and primitive sympathetic cells (Hervonen et al).^[22] These cells are small circular cells with a darkly stained nucleus. Studies conducted by Ram et al,^[14] reported that the chromaffin cells appear between 21 and 25 weeks of gestational age; our study also produced similar results. Turkel et al,^[17] observed that the maximum number of neuroblastic nodules was observed between 17 and 20 weeks of gestation; in our study, we also reported similar observations. Coupland et al,^[21] and Hervonen et al,^[22] had documented that the reduction in these cells after the 20th week of gestation was attributed to the conversion of these cells to the chromaffin cells and the sympathetic ganglionic cells.

CONCLUSION

Our observations of the fetal suprarenal gland showed three different zones: the fetal zone, the zona glomerulosa, and the zona fasciculata. According to the definitive cortex's arrangement, the cells in the zona glomerulosa layer changed from being isolated to being grouped into a distinct glomerulus-like structure. The cells in the fascicular layer were grouped in a fascicular arrangement, separated by sinusoidal spaces. At 12 weeks, 1/9 weeks, and 1/4 weeks, respectively, the definitive cortical to fetal cortex pattern changed as the pregnancy continued.

Neuroblastic cells from neural crest cells invaded the capsule around the 12th week. By the 24th week, the nodules had spread out. Neuroblastic cells were observed migrating from the capsule toward the central blood vessels. They were separated into chromaffin cells and sympathetic neurons.

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Conflicts of interest

There are no conflicts of interest.

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